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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,664	12/05/2003	Hidenobu Yaku	2003_1763.A	5974

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,664	YAKU ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 23-36* is/are pending in the application.

4a) Of the above claim(s) *23-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 5/24/2007. Currently Claims 1-19, 23-36 are pending. Claims 23-36 are withdrawn.

2. This action contains rejections necessitated by amendment for Claims 1-19.

3. This action is NONFINAL.

Withdrawn Rejections

4. The rejection of Claims 1-19 made under 35 USC 103(a) in sections 8-11 of the previous office action is moot based on amendments to the claims. Specifically the reply points to Delrio-Lafreniere reference wherein Delrio-Lafreniere et al. teaches away from the claimed invention (p. 13 last paragraph).

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Steinborn et al. (PCT Application WO 99/40219 August 12, 1999).

With regard to Claim 1, Zhou et al. teaches a method of detection of single nucleotide polymorphisms (SNPs) in a target (determining a base type) (Abstract). With regard to Claim 1a, Zhou et al. teaches a reaction solution comprising a target, SNP primers, theromostable DNA polymerase, and dNTPs (p. 4 1st column Allele-specific extension reaction). Zhou et al. teaches dividing the sample into two solutions so that one solution contains the wildtype primer (first base type determination primer) and the other solution contains the mutant primer (second base type determination primer) (Figure 1). With regard to Claim 1b, Zhou et al. teaches hybridization of the primer to the target and determination of a SNP (Figure 2 p. 4). With regard to Claim 1c, Zhou et al. teaches a primer which is uncomplimentary at the third position. Zhou et al. teaches

there is a complementary region adjacent to the uncomplimentary region (Figure 2 p. 4). Zhou et al. teaches detecting luminescence when the primer is extended (degree of progress (Figure 2 p. 4). Zhou et al. teaches determining heterozygosity or homozygosity of the allele. Zhou et al. teaches that the allele can be detecting on each strand (p. e93 2nd column 1st paragraph). Zhou et al. teaches that the frequency of the mutant be detected on each strand by detecting the intensity values of the mutant allele and the wild type allele in each sample. Therefore, Zhou et al. determines in a given sample if the allele is present on both strands (homozygous) or only one strand (heterozygous).

With regard to Claim 2, Zhou et al. teaches using a thermostable DNA polymerase without exonuclease activity (p. 4 1st column Allele-specific extension reaction).

With regard to Claim 3, Zhou et al. teaches the primer and the target are DNA (Abstract).

With regard to Claim 4, Zhou et al. teaches performing a PCR reaction with a forward and reverse primer (p. 4 1st paragraph).

With regard to Claim 5, Zhou et al. teaches the base difference is determined by the extension of the primer wherein no extension provides no measurable luminescence (Figure 2 p. 4).

With regard to Claim 6, Zhou et al. teaches the SNP typing can be performed by measuring pyrophosphate or by gel-based electrophoresis (Table 2 p. 9).

With regard to Claim 7, Zhou et al. teaches measuring pyrophosphate (Ppi) (Abstract). With regard to Claim 8, Zhou et al. teaches measuring the amount of Ppi generated (Figure 1). With regard to Claim 9, Zhou et al. teaches determination of the SNP (base sequence determination) and determining if the SNP is an A, G, C, or T (base type) (Figure 3 p. 5).

However, Zhou et al. does not teach a method in which the second and third positions are uncomplimentary. Zhou et al. only teaches the third position is uncomplimentary.

Steinborn et al. teaches a method pf quantification of nuclide acid sequences by detecting allelic differences using allelic specific primers (abstract). Steinborn et al. teaches the primer is designed such that at the 3' end the base either matches the wildtype or the mutant (p. 11 lines 20-25). Steinborn et al. teaches that at the 3' end two or more mismatches between position –2 to –10 of the 3' end are designed (p. 12 lines 18-20).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the SNP detection method of Zhou et al. to include primers designed with intentional mismatches at the 3' end including mismatches at the penultimate and antepenultimate bases (2^{nd} and 3^{rd} positions in the uncomplimentary region) on the 3' end of the primer because Steinborn et al. teaches that two or more mismatches between positions –2 to –10 of the 3' end can be designed. The ordinary artisan would be motivated to have mismatches at the penultimate and antepenultimate bases because Steinborn et al. teaches mismatches

at the 3' end additional mismatches leads to enhanced primer instability (p. 12 lines 5-10). Steinborn et al. teaches that due to this increased primer instability no amplification of the mismatch allele takes place (p. 12 lines 5-10). The ordinary artisan would be motivated to make mismatches in the primers in order to decrease mispriming of the primer to the wildtype or mutant allele. The mismatches on a primer designed such that the 3' end is identical to the wildtype would not prime to the mutant allele.

7. Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Steinborn et al. (PCT Application WO 99/40219 August 12, 1999) as applied to Claims 1-9 and in further view of Scopes et al. (Analytical Biochemistry 1972 Vol. 49 p. 88) and Benkoel et al. (The Journal of Histochemistry and Cytochemistry 1976 Vol. 24 p. 1194).

Zhou et al. teaches measuring ppi, however, neither Zhou et al. nor Steinborn et al teach the steps of converting pyrophosphoric acid into inorganic phosphoric acid.

With regard to Claim 10, Scopes et al. teaches a method of detecting the conversion of organic phosphate into inorganic phosphate (p. 88 1st paragraph). Scopes et al. teaches a method of using glyceraldehydes-3-phosphate (p. 88 1st chemical formula). Scopes et al. teaches this gets converted into 1,3-diphosphoglycerate concomitant with the reduction of coenzyme to NADH (nicotinamide adenine dinucleotide) (p. 88). Scopes et al. teaches providing glyceraldehydes 3-phosphatedehyrogenase (p. 89 1st paragraph).

With regard to Claims 10 and 11, Benkoel et al. teaches using ferricyanide as an electron acceptor (Abstract). With regard to Claim 12, Benkoel et al. teaches determining the prices localization of various reactions in different electron transfer chains determined by using different ferricyanide concentrations and intermediate electron carriers such as diaphorase (Abstract).

Therefore it would have been prima facie obvious to one of skill in the art at the time of the invention to modify the method of Zhou et al. and Steinborn et al. to incorporate the method steps of pyrophosphoric conversion as taught by Scopes et al. and Benkoel et al. The ordinary artisan would have been motivated to incorporate the method steps of pyrophosphoric acid conversion as taught by Scopes et al. and Benkoel et al. in order to maximize the detection of the SNPs in the reaction. Scopes et al. teaches a rapid detection of phosphate liberation in samples (p. 88 last paragraph). The skilled artisan would be motivated to use the steps as taught by Scopes et al. to quickly detect the conversion of inorganic phosphorus in a sample. Further, Benkoel et al. teaches using copper ferrocyanide to observe electron transfer without staining (p. 11944 1st paragraph). The skilled artisan would be motivated to use both ferrocyanide and diaphorase to determine the precise localization of reactions (Abstract).

8. Claims 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Steinborn et al. (PCT Application WO 99/40219 August 12, 1999) as applied to Claims 1-9 and in

further view of Bille et al. (herein referred to as Bille, 1992, Phys. Plantarum, vol. 84, pages 250-254).

Neither Zhou et al. or Steinborn et al. teach the measurement of pyrophosphate *specifically* where the pyrophosphate is detected by applying part of the amplification reaction to a membrane system that contains pyrophosphatase and measuring the change in H+ concentration.

Bille teaches that a quantitative relationship can be obtained between pyrophosphate concentration and a change in pH inside a vesicle membrane that contains H+-pyrophosphatase when pyrophosphate is added to a system containing vesicle membranes (claims 14, 15, and 19, see page 251, column 1, all of para 4, page 252, column 2 all of para 1, and Figures 2 and 3 of Bille). Bille teaches that the change in pH in this system is measured by a change in the absorbance of acridine orange (claims 16 and 17, see page 251, column 1, all of para 4, page 252, column 2 all of para 1, and Figures 2 and 3 of Bille). Bille also teaches that a positive current into a vacuole containing pyrophosphatase caused by a change in pH can be detected upon addition of pyrophosphate to vacuoles by the patch-clamp technique (claim 18; see page 252, column 2, all of para 4, page 253, column 1, all of para 1, and Figure 6 of Bille).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of detecting pyrophosphate in SNP detection of Zhou et al. and Steinborn et al. by subjecting the pyrophosphate to the system of vesicle membranes having pyrophosphatase and measuring the change in pH inside the vesicles or detecting such a pH change by the patch-clamp technique in

view of the teachings of Bille for the purpose of developing a sensitive method of pyrophosphate detection in SNPs as taught by Zhou et l. and Steinborn et al. The ordinary artisan would have a reasonable expectation of success that using the membrane associated pyrophosphatase system with a pH sensitive dye or path-clamp method taught by Bille to measure pyrophosphate levels in the SNP detection of Zhou et al. and Delrio-Lafreniere et al. would result in a sensitive and effective measurement of pyrophosphate, as evidenced by Figures 3 and 6 of Bille, released during the extension reaction in the method taught by Zhou et al. and Steinborn et al. because Bille teaches a direct quantitative relationship between pyrophosphate levels and resulting pH change in vesicle membranes as measured by a pH sensitive dye or the patch-clamp technique.

Conclusion

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

J. Goldberg
8/15/07